*REMARKS/ARGUMENTS*

*The Pending Claims*

Claims 1-27 are pending and are directed to a liposome (claims 1-19, and 22-24), a composition comprising the liposome (claim 20), an agent comprising the liposome (claim 21), and a method of producing the liposome (claims 25-27).

Claims 25-27 have been labeled as withdrawn because the Examiner considers that the claims are directed to a non-elected invention. Since claims 25-27 are directed to a method of producing the elected product, Applicants request that any withdrawn claims be rejoined in accordance with the provisions of MPEP § 821.04 upon the allowance of one or more of the elected product claims to the extent such withdrawn claims depend from or otherwise include all of the limitations of an allowed claim. In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims should be withdrawn, and the rejoined process claims should be fully examined for patentability in accordance with 37 CFR § 1.104.

*Amendments to the Claims*

Claim 1 has been amended to recite that the particle size of the liposome is more than 10 nm. This amendment is supported by the specification at paragraph 0038, which discloses that the particle size of the primary emulsion is 10 nm to 150 nm. Since the particle size of the primary emulsion corresponds to the inner diameter of the resultant liposome, the particle size of the liposome must be 10 nm or more.

Claim 25 has been amended to depend from claim 1.

No new matter has been added by way of these amendments to the claims.

*Summary of the Office Action*

The Office maintains the rejection of claims 1-5, 7, 11-16, 20, and 21 and newly rejects claims 22-24 under 35 U.S.C. § 102(b) as allegedly anticipated by Modi (U.S. Patent 6,193,997).

The Office maintains the rejection of claims 1-7 and 9-24 under 35 U.S.C. § 103(a) as allegedly obvious in view of Modi and Slater et al. (U.S. Patent Application Publication 2003/0133973). Additionally, the Examiner maintains the rejection of claims 1-5, 7, 8, and 11-24 under 35 U.S.C. § 103(a) as allegedly obvious in view of Modi and Tagawa et al. (EP 1170018).

Reconsideration of these rejections is hereby requested.

*Discussion of the Anticipation Rejection*

The Office maintains its contention that the Modi reference anticipates the claims by disclosing a liposome with a particle size of 10 nm or less, which contains a ligand and triolein. The anticipation rejection is traversed for the following reasons.

A liposome, such as that of the pending claims, has a lipid bilayer membrane, as well as an inner sphere (i.e., internal cavity). As discussed in the previous "Reply to Office Action," the Modi reference discloses a "mixed liposome," which differs in size from the liposome of the pending claims (see pages 7-8 of the "Reply to Office Action" dated June 8, 2009).

Applicants have amended the pending claims to include a lower limit to the particle size to further distinguish the claimed liposome from the "mixed liposome" of the Modi reference. In particular, Applicants have amended the pending claims to recite that the particle size of the liposome is more than 10 nm, which is larger than the particle size of the "mixed liposome" of the Modi reference.

The inventive liposome can be prepared in a stepwise manner by preparing a W/O emulsion (primary emulsion) and then preparing a W/O/W emulsion (double emulsion). One of ordinary skill in the art recognizes that the particle size of the primary emulsion corresponds to the *inner* diameter of the resultant liposome. The specification discloses that the particle size of the primary emulsion is 10 nm to 150 nm (see paragraph 0038). Accordingly, the particle size of the resultant liposome is greater than the particle size of the primary emulsion (i.e., more than 10 nm).

Applicants note that claims 22-24 further define the liposome of claim 1 by reciting a particular process by which the liposome is produced. Particular aspects of the process further define features of the inventive liposome. For example, claim 22 recites that the particle size of the primary emulsion is 10 nm to 150 nm, and claim 23 recites 30 nm to 100 nm. As discussed above, the particle size of the primary emulsion corresponds to the inner diameter of the resultant liposome. Therefore, by reciting the particle sizes of the primary emulsions, claims 22 and 23 further define the particle size of the resultant liposome.

Since the particle size of the claimed liposome is greater than that of the "mixed liposome" of the Modi reference, the Modi reference cannot be considered to anticipate the pending claims. Therefore, Applicants request that the anticipation rejection be withdrawn.

*Discussion of the Obviousness Rejections*

The Office maintains its contention that it would have been obvious for one of ordinary skill in the art to arrive at the claimed invention in view of the Modi reference and either of the Slater or Tagawa references. Furthermore, in response to Applicants' argument of unexpected beneficial properties, the Office indicates that there is no objective evidence of record to show the inventive liposomes have advantageous properties when compared to the "mixed liposome" of the Modi reference. The obviousness rejections are traversed for the following reasons.

The present invention, as defined by the pending claims, is directed to a liposome encapsulating a water-soluble substance in an internal cavity thereof, wherein the liposome has a particle size of more than 10 nm and 300 nm or less and contains a triglycerol, as well as a method of producing such a liposome.

As discussed above, the Modi reference discloses a "mixed liposome," which differs from the inventive liposome and those disclosed in the Slater and Tagawa references based on particle size. The "mixed liposome" has a particle size of 10 nm or less. In contrast, the Slater reference discloses liposomes with particles sizes of 40-250 nm (see, e.g., paragraph 82 of the Slater reference), and the Tagawa reference discloses liposomes with particles sizes of 20-500 nm (see, e.g., paragraphs 22-23 of the Tagawa reference). Accordingly, the Modi reference and the Slater and Tagawa references are directed to two different products ("mixed

liposomes" versus conventional liposomes), such that one of ordinary skill in the art would not have had any reason to combine the disclosures of these references, let alone in the particular manner that would result in the claimed invention.

As discussed in Applicants' "Reply to Office Action" dated June 8, 2009, the existence of unexpected benefits attendant the present invention further rebuts the obviousness rejections. The inventors discovered that by using triglycerol as one of the liposome-forming lipids, an unexpected and advantageous improvement on the stability of the liposome results relative to the liposomes known in the art. Additionally, particle size variation is significantly reduced, which results in the ability to avoid contamination with liposomes of larger particle sizes. Moreover, a higher rate of drug encapsulation into the liposome is achieved with use of the inventive liposome.

The "Declaration under 37 C.F.R § 1.132 of Toshiaki Tagawa, Ph.D." (submitted herewith) describes an experiment demonstrating the advantageous properties of the inventive liposome when compared to the mixed liposome of the Modi reference. In particular, the experiment described in the Rule 132 Declaration demonstrates that the rate of encapsulation of the "mixed liposome" of the Modi reference is approximately 1%, which is much lower than that of the inventive liposome. As demonstrated by the Examples in the specification, each of the inventive liposomes had an encapsulation rate of 55% or higher (see Examples 2-13, 15-20, and 22). Thus, the inventive liposome has remarkably advantageous properties as compared to the "mixed liposome" of the Modi reference.

Furthermore, the advantageous results achieved using the inventive liposome were unexpected in view of the teachings in the art. The existence of the unexpected benefits attendant the present invention supports the unobviousness of the present invention and rebuts the obviousness position recited in the Office Action, even if the combination of the disclosures of the cited references are considered to properly establish *prima facie* obviousness.

For the above-described reasons, the obviousness rejections should be withdrawn.

*Conclusion*

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

John Kilyk, Jr., Reg. No. 30,763
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson Avenue
Chicago, Illinois 60601-6731
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

Date: October 13, 2009